UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,010	07/16/2003	Joseph Monforte	47-030010US	1659

22798 7590 02/10/2005

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,010	MONFORTE, JOSEPH	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *51-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/4/03; 11/2/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Remark

The Group and/or Art Unit location of your application in the PTO has been assigned to Art Unit 1637. All further correspondence regarding this application should be directed to Examiner Young J. Kim, whose Group Art Unit is 1637.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-24 and 26-50 (in part) in the reply filed on October 26, 2004 is acknowledged. The traversal is on the ground(s) that the claims share the same special technical features and have shared steps. While the term, "special technical feature," is reserved for PCT applications and applications filed under National Stage (371), and does not apply to the instant application, upon reconsideration, Groups I and II will be rejoined for prosecution.

Applicants' traversal does not include any arguments toward the rejoinder of Group III. However, even if the arguments were to be made, the arguments would not be found persuasive as the methods of Groups I and II can be done by any of the known microarrays in the industry and not limited to the array of Group III.

Claims 51-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 26, 2004.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-50 are under prosecution therefore.

Priority

The Office acknowledges the priority claim made under 35 U.S.C. 119(e) to provisional application no. 60/397,393, filed on July 19, 2002.

Information Disclosure Statement

The IDS filed on December 1, 2003 and October 29, 2004 are acknowledged.

The signed copies of their PTO-1449 are attached hereto.

Drawings

The drawings received on July 16, 2002 are acceptable.

Specification

The specification is objected to by the Examiner because it makes reference to an URL on the internet. For example, section [0093] of page 22 contains active hyperlinks. While information on web-address is accessible, the embedded hyperlinks and/or other forms of browser-executable code are impermissible and require deletion. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference.

If the subject matter which is improperly incorporated by reference is directed to nonessential material (illustrating the state of the art), the deletion will probably not be considered as new matter. However, if the subject matter which is improperly incorporated by reference is directed to essential material, applicant will be required to amend the specification to include the subject matter incorporated. The amendment must be accompanied by an affidavit or

declaration executed by the applicant stating that the amendatory material consists of the same material incorporated by reference.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35 and 36 (by way of dependency) are indefinite because the claim recites steps prefaced by the phrase, "the method of claim 1 or 25, comprising." It is indefinite as to whether the recited step is conducted ***instead*** of the steps recited in claims 1 and 25 ***or*** the recited steps are ***additional steps*** to claims 1 and 25. Replacing the word, "comprising" to "further comprising" would overcome this issue.

Additionally, if the latter interpretation is assumed, Applicants are advised to clarify which of the steps (for dependency on claim 1, steps (a)-(g); for dependency on claim 25, steps (a)-(c)) the additional steps of claim 35 are to further limit.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-13, 15, 17, 21-27, 33-39, 42-45, 49, and 50 are rejected under 35 U.S.C. 102(a) as being anticipated by Thomas et al. (Molecular Pharmacology, 2001, vol. 60, pages 1189-1194, IDS reference #16).

Thomas et al. disclose a method of identifying toxicologically predictive gene sets using cDNA microarrays, wherein the method comprises the steps of:

a) contacting a plurality of biological samples with a plurality of members of a compound library (page 1190, 1st column, *Animals and Treatment*);

b) obtaining an expressed RNA sample from each of the plurality of biological samples (page 1190, 1st column, *RNA isolation*);

c) arraying a plurality of nucleic acids (in the form of a cDNA microarray) (page 1190, 1st column, *cDNA Microarray Construction*);

d) hybridization of the probes to the cDNA microarray (page 1190, 2nd column, 1st paragraph);

e) quantitating a signal produced from the hybridization reaction (page 1190, 2nd column, 2nd paragraph);

f) detecting at least one signal that differs from control hybridization (page 1190, 2nd column);

g) entering the quantitated hybridization signal into a database (page 1192, 1st column, Figure 1), which states that the most informative gene is employed in a Bayesian classification, neccearily requiring a computer system housing the data (or database).

Therefore, Thomas et al. anticipate claims 1, 3, 25, 34, 49, and 50.

The biological samples is contacted with various members of compounds (Table 1, page 1190, bottom), anticipating claims 2 and 17.

The isolated mRNA transcripts are disclosed as being amplified via reverse transcriptase reaction (page 1190, 1st column, *cDNA Microarray Construction*), producing cDNA probes anticipating claims 4 and 43, wherein said cDNA probes are labeld with Cy3 and Cy5 fluorescent moiety (page 1190, 2nd column, 2nd paragraph), anticipating claims 44 and 45.

The control biological sample are subject to the compound treatment over a time period (page 1190, 2nd column, 4th paragraph) which would necessarily include 0 time point, anticipating claim 5.

By way of the differential expression pattern of select arrayed genes (represented by their fold difference), the quantitated hybridization would necessarily be different (page 1190, 2nd column, *Data Reduction*), anticipating claims 6 and 7.

Statistical Analysis is conducted on all quantitated signal (page 1191, 1st column, *Statistical Classification Analysis*), anticipating claims 8-10.

The microarray employed by Thomas et al. comprises at least 1200 probe sequences (page 1190, 1st column, bottom paragraph), anticipating claim 11.

The RNA are isolated from mice cells and frozen tissues (page 1190, *RNA Isolation*), anticipating claims 12, 13, and 15.

The method employed by Thomas et al. first isolates total RNA, followed by their mRNA extraction (page 1190, 1st column, *RNA Isolation*), anticipating claims 21 and 22.

The cDNA microarray employed by Thomas et al. is disclosed as being made of amplified cDNAs and expressed sequence tags (page 1190, 1st column, *cDNA Microarray Construction and Analysis*), anticipating claims 23 and 24, wherein said amplification is disclosed as being polymerase chain reaction (PCR), anticipating claims 26 and 27.

The cDNA microarray is disclosed as being made via spotting (or arraying) each cDNA clones on the array (Figure 4), anticipating claims 33 and 36.

The probes which are hybridized to the cDNA microarray is disclosed as comprising probes which are specific for housekeeping genes (page 1190, 2nd column, top paragraph), anticipating claim 35.

The probes comprises sequences related to inflammation, hypoxia (Table 2 and Abstract), anticipating claim 37.

The cDNA microarray is disclosed as comprising a glass surface (page 1190, 1st column), anticipating claims 38, 39, and 42.

Therefore, Thomas et al. anticipate the invention as claimed.

Claims 1-15, 17-26, 30-34, 37-45, and 50 are rejected under 35 U.S.C. 102(a) or alternatively, 102(e) as being anticipated by Mohanlal (WO 02/40717 A2, published May 23, 2002, filed November 14, 2001, priority November 14, 2000 under amended AIPA – IDS reference # 5).

Mohanlal discloses a method of screening a chemical (or compound) to identify a compound with a physiological effect on a biological sample, said method comprising the steps:

a) contacting a plurality of biological samples with a compound (page 4, lines 10-11);

b) obtaining an expressed RNA sample from each of the biological samples (page 5, line 5);

c) arraying a plurality of nucleic acids corresponding to the plurality of expressed RNAs (page 6, lines 7-11 and page 12, lines 13-16);

d) hybridizing a plurality of defined sequence probes comprising a signal moiety and quantitating the signals (page 17, lines 4-6; page 18, lines 15-17; and page 19); and

e) storing the hybridization signal data into the computer (page 26, lines 24-56) and the data is mined, evidencing that the data is stored in the computer.

Therefore, Mohanlal anticipates claims 1, 17, and 37-45.

Mohanlal discloses that a plurality of compounds are contacted with a plurality of chemicals (page 25, lines 13-15; page 26, lines 26-28), anticipating claim 2.

The method of Mohanlal employs RNA extraction from samples which are exposed to a chemical entity and samples which are not exposed to chemical entity (or control sample), from which subtractive hybridization is conducted to identify genes which are only up or down regulated by the applied chemical entity (page 11, lines 7-10), thereby anticipating claims 3-10.

The microarray employed by Mohanlal is disclosed as comprising a plurality of immobilized nucleic acids (page 12, lines 13-15; page 17, lines 4-6; page 26, lines 24-25), anticipating claim 11.

The samples employed by Mohanlal is disclosed as being cell isolate (PBMC) from patients, anticipating claims 12 and 15.

Mohanlal discloses that mRNA is extracted from a minimum of 10 million successfully transduced cells that are treated with drugs and the libraries, pooled (page 25, lines 8-15; page 26, lines 26-28), anticipating claims 18-27, 30-34. The cell samples are also disclosed as being treated with zinc finger proteins prior to their treatment with the chemical (page 6, lines 5-6), anticipating claims 13 and 14.

The hybridization pattern of the samples are disclosed as being compared to a reference pattern (page 6, lines 25-27; page 11, line 11) anticipating claim 50.

Therefore, Mohanlal anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al. (Molecular Pharmacology, 2001, vol. 60, pages 1189-1194, IDS reference #16).

The teachings of Thomas et al. have been discussed above.

Thomas et al. do not explicitly conduct their method for at least 500, or at least 1000, or at least 10,000 biological samples, each of which biological samples is treated with a different member of a compound library.

Thomas et al., however, do suggest the below:

"The toxicological categories selected in our study primarily reflect the model compounds that toxicologist have studied extensively over the last decade and represent ***only a small percentage of the 70,000 chemicals in the commerce today***." (page 1194, 2nd paragraph, bottom).

Therefore, based on such knowledge and suggestion, one of ordinary skill in the art would have been motivated to apply the teachings of Thomas et al. to any number of biological samples, each of which is treated with any of the known chemicals which are biological significant. One of ordinary skill in the art would have had a reasonable expectation of success at such application as Thomas et al. clearly suggests that there is a large number of biologically significant chemicals that have yet to be studied.

Additionally, the use of microarray for screening compounds in samples, be it eukaryotic or prokaryotic, has been well-established in the art of microarray, for the advantage of high throughput capacity.

Therefore the invention as claimed is obvious over Thomas et al.

Claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas et al. (Molecular Pharmacology, 2001, vol. 60, pages 1189-1194, IDS reference #16) in view of Wang et al. (U.S. Patent No. 5,922,617, issued July 13, 1999).

The teachings of Thomas et al. have been discussed above.

The microarray employed by Thomas et al. is a 2-dimensional glass array, and not beads, spheres or optical fibers.

Wang et al. disclose a microarray substrate (column 2, lines 60-61), wherein said substrate is disclosed as being silicone, magnetic beads, etc. (column 5, line 30-64).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Thomas et al. to employ a microarray, wherein the solid-substrate of microarray is any of the well-known solid substrates, including beads, as evidenced by Wang et al.

Additionally, the MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that a wide array of substrates were employed in the art of microarray technology, as evidenced by Wang et al., one of ordinary skill in the art would have had a reasonable expectation of success at employing any of the well-known solid substrate materials for the purpose of making a microarray, rendering the claims obvious over the cited references.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Claims 16, 35, 36, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mohanlal (WO 02/40717 A2, published May 23, 2002, filed November 14, 2001, priority November 14, 2000 under amended AIPA – IDS reference # 5) in view of Chenchik et al. (WO 99/35289, published July 15, 1999, IDS reference # 10).

Mohanlal does not explicitly state that the biological sample comprise prokaryotic samples.

Mohanlal dose not explicitly state that housekeeping genes are employed as controls for the purpose of normalizing the hybridization results.

While the nucleic acid molecules which are arrayed on a microarray are initially amplified prior to their immobilization, Mohanlal does not explicitly state that the amplification is performed by multiplex PCR using a plurality of gene specific primers, nor the gene specific primers further comprise a universal priming sequence.

Mohanlal does not explicitly state that the plurality of defined sequence probes comprise an amplifiable signal element detected by the members recited in the Markush group of claims 46-48.

Chenchik et al. disclose a well-known practice of employing control nucleic acids in a microarray for the purpose of normalizing hybridization results (page 16, lines 7-9).

Chenchik et al. disclose a method of detecting target sample on a microarray, wherein the probes are labeled with moieties, wherein the moieties are listed as being any one of fluorescent moieties (page 13, lines 31-32; page 14, lines 1-5), members of specific binding pair such as biotin, fluorescein, digoxigenin, antigen, polyvalent cations (page 14, lines 8-10), where the members specifically bind to ***additional members of the signal producing system, where the additional members provide a detectable signal either directly or indirectly*** (page 14, lines 10-14), thus hybridization signal amplification method, anticipating claims 46-49.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mohanlal with the teachings that are well-known in the art, as evidenced by Chenchik et al. to arrive at the claimed invention for the following motivation.

The use of microarray for screening compounds in samples, be it eukaryotic or prokaryotic, has been well-established in the art of microarray, for the advantage of high

throughput capacity. Thus, one of ordinary skill in the art would have been easily motivated to modify the method of Mohanlal to employ the advantage of using control nucleic acids for the expressed benefit of normalizing hybridization results, as well as employing well-known labeling schemes, further evidenced by Chenchik et al. with a clear expectation of success.

While Mohanlal is not explicit in their disclosure as to whether an internal control nucleic acid was involved in their assay, one of ordinary skill in the art would have had a reasonable expectation of their use nevertheless, as the use of control nucleic acids have been well-established in the art of microarrays.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

MPEP, at 2143.02 states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that the claimed modifications - control nucleic acids and labeling techniques – have been well known in the art, it is clear that one of ordinary skill in the art would have had a reasonable expectation of success at the claimed modification.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mohanlal (WO 02/40717 A2, published May 23, 2002, filed November 14, 2001, priority

November 14, 2000 under amended AIPA – IDS reference # 5) in view of Shuber (U.S. Patent No. 5,882,856, issued March 16, 1999).

The teachings of Mohanlal have already been discussed above.

Mohanlal does not explicitly teach a multiplex amplification involving a plurality of gene specific primer, as well as said gene primers further comprising a universal sequence.

Shuber discloses a multiplex amplification procedure involving the use of gene specific primers comprising a universal sequence (column 2, lines 54-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the multiplex amplification method employed by Shuber in the amplification step of Mohanlal for the motivation/advantage of simultaneously generating amplicons of multiple target nucleic acids which is known in the art as reducing time, contamination as well as reagent costs.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637

by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
2/7/05

YOUNG J. KIM
PATENT EXAMINER

yjk